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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,428	SIMMONS, LAURA	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-128* is/are pending in the application.

4a) Of the above claim(s) *75-81 and 128* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-74 and 82-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/06; 7/11/05;*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-128 are pending.

2. Applicant's election with traverse of Group I, Claims 1-74 and 82-127, drawn to a method for producing an antibody or antigen binding fragment in high yield in cell culture, the antibody or variable domain is an anti-VEGF antibody, filed 2/13/06, is acknowledged. The traversal is on the grounds that it would not unduly burdensome to search a genus claim and more than one species based on the related structural and functional properties of the claimed method directed to a genus of antibodies. Further, these groups as they are classified in the same class and subclass. A search of these groups as they are classified in the same class and subclass would include references for antibodies for different specificities. Applicants further traverse the restriction requirement to the subject matter of the group III and IV claims because the Examiner has not established that the search of the subject matter of both groups would be unduly burdensome. Applicants request an interview with the Examiner and his supervisor before the restriction is finalized.

This is not found persuasive because of the reasons set forth in the restriction mailed 1/12/06.

With respect to the argument that the restriction requirement of groups I (drawn to a method for producing an antibody or antigen binding fragment in high yield in cell culture, the antibody or variable domain is an anti-VEGF antibody) and II (drawn to a method for producing an antibody or antigen binding fragment in high yield in cell culture, the antibody or variable domain is an anti-IgE antibody) should be examined together with no undue burden, it is burdensome to search more than one group in one application This is because the method of producing VEGF antibody or antigen binding fragment thereof in high yield by replacing the heavy chain framework region (FR1) subgroup III of anti-VEGF with the different amino acids found at the corresponding FR1 position of a human subgroup I enhanced the yield of the antibody. However, the same method applies to making IgE antibody resulted in a decrease rather than an increase in yield (see specification page 83). It is burdensome to search a genus claims having any combination of amino acid substitutions in FR1, FR2, FR3, FR4 and mixture thereof as well as amino acids substitution within the CDRs from different immunoglobulin

heavy and light chains. Further, a prior art search also requires a literature search. It is a burden to search more than one invention.

With respect to the argument that the restriction requirement of groups III (drawn to VEGF antibody) and IV (drawn to IgE antibody) is improper, as was stated in the previous office action, they differ structurally, i.e., different combination of CDRs from heavy and light chains. These antibodies differ functionally binding to VEGF as opposed to binding to IgE and cannot be used together or interchangeably. Even though in some cases the classification is shared, a different field of search would be required based upon the structurally distinct products and binding specificity of the antibodies. A prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention. Therefore restriction for examination purposes as indicated is proper.

With respect to telephonic interview for restriction requirement, interview prior to first official action is ordinary granted only in continuing application. A request to interview for all other applications before the first action is untimely and will not be acknowledged if mitten, or granted if oral. See 37 CFR 1.33(a).

Therefore, the requirement of Group 1 and Groups 3-4 is still deemed proper and is therefore made FINAL.

3. Claims 75-84 and 128 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-74 and 82-127, drawn to a method for producing an antibody or antigen binding fragment in high yield in cell culture, the antibody or variable domain is an anti-VEGF antibody, are being acted upon in this Office Action.

5. The disclosure is objected to because (1) incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 68, line 11 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent

application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database.

6. Claims 4, 13, 28, 40, 58, 85, 88, 107, and 116 are objected to for reciting non-elected embodiment.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-74 and 82-127 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for improving the yield of anti-VEGF antibody or antigen binding fragment thereof production in cell culture such as the methods discloses on pages 79 and 87, **does not** reasonably provide enablement for a method of producing any antibody or any antigen binding fragment in high yield comprising a) expressing a variable domain of the antibody or antigen binding fragment comprising any one or more modified framework region (FR) in a host cell as set forth in claims 1-24, and 50-70, (2) a method for preparing any humanized antibody or antigen binding fragment as set forth in claims 25-37, and 71-73, and (3) a method for improving the yield of any antibody or antigen binding fragment in cell culture comprising expressing any heavy chain variable domain of the antibody or antigen binding fragment comprising any one or more modified FR, or modified at least one FR sequence of any variable domain of any antibody or antigen binding fragment such that it is at least 50% identical to any corresponding FR sequence of any selected subgroup consensus sequence as set forth in claims 38-49, 74, and 82. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. This rejection encompasses four distinct issues, which will be addressed in turn:

(a) Enablement is not commensurate in scope with claims as how to produce any antibody or antigen binding fragment in high yield by expressing a variable domain of the antibody or antigen binding fragment comprising at least any one modified FR in a host cell.

In order to produce any antibody in high yield in culture, the amino acid sequences with the appropriate sequence identifier (SEQ ID NO) or the corresponding polynucleotides of immunoglobulin heavy and light chains including the framework regions are required. Further, the location and the type of amino acids to be substituted within the framework regions i.e., FR1, FR2, FR3 and FR4 of immunoglobulin heavy and light chain are required. There is insufficient guidance as to which amino acids within which framework regions 1 through 4 of the heavy chain and the light chain to be substituted for which amino acid from the corresponding framework region of which human subgroup variable consensus sequence. Although the positions in the heavy chain FR1 are recited in claims 19-20, and 42-43, the type of amino acids to be substituted is not recited in those claims. Accordingly, an undue experimentation would be required to determine how to practice the claimed invention.

The specification discloses only a method for improving the yield of anti-VEGF antibody or antigen binding fragment thereof in high yield in cell culture comprising the step of: a) replacing the human heavy chain framework regions 1(FR1) subgroup III consensus sequence of SEQ ID NO: 3 with the human heavy chain FR1 subgroup I consensus sequence of SEQ ID NO: 1 at those position where the residues differ, b) expressing the variable domain of the VEGF antibody or antigen binding fragment thereof comprising the human heavy chain FR1 subgroup I consensus sequence of SEQ ID NO: 1, and recovering the antibody or antigen binding fragment thereof (see page 76). (2) the said method wherein the antibody heavy chain variable region (HVR1) consisting of the amino acid sequence selected form the group consisting of GYTFTNYGIN (SEQ ID NO: 14), GYDFTHYGMN (SEQ ID NO: 18) and GYSITSGYSWN (SEQ ID NO: 19). The specification also discloses a method for preparing a humanized VEGF antibody or antigen binding fragment thereof, comprising (i) substituting the heavy chain FR1 of subgroup III GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO: 18) of anti-

VEGF with FR1 from subgroup I consensus sequence GYTFTSYAIS of SEQ ID NO: 15 at those position where the residues differ, b) expressing the variable domain of the VEGF antibody or antigen binding fragment thereof comprising the human heavy chain FR1 subgroup I consensus sequence of SEQ ID NO: 15, and recovering the antibody or antigen binding fragment thereof (see page 79). The specification also discloses a method for improving the yield of anti-VEGF antibody or antigen binding fragment thereof in cell culture by substituting at least two amino acid residues in FR1 heavy chain of SEQ ID NO: 3 wherein the amino acid residue E at position 6 is substituted for Q and amino acid residue A at position 23 is substituted for K wherein the substitution increases the yield of assembled anti-VEGF antibody about two fold or amino acid residue E at position 1 is substituted for Q, E at position 6 is substituted for Q, L at position 11 is substituted for V, Q at position 13 is substituted for K, L at position 18 is substituted for V, R at position 19 is substituted for K and A at position 23 for K (page 87).

(b) Enablement is not commensurate in scope with claims as how to produce any antibody or antigen binding fragment in high yield by expressing a variable domain of the antibody or antigen binding fragment comprising expressing at least one modified framework regions (FR) from *light chain* wherein the modified FR has a substitution of at least one amino acid position with a different amino acid found at the corresponding FR of a human subgroup variable domain consensus sequence that has a **HVR1** (heavy chain variable region 1) and/or **HVR2** (heavy chain variable region 2 (claims 1, and 7).

The specification discloses only replacing the human *heavy chain* framework regions 1(FR1) subgroup III consensus sequence of SEQ ID NO: 3 in the specific VEGF antibody with the human *heavy chain* FR1 subgroup I consensus sequence of SEQ ID NO: 1 at those position where the residues differ.

The specification does not disclose replacing at least one amino acids in at least one framework region of the *light chain* for different amino acid found at the *heavy chain* FR of a human subgroup variable domain consensus sequence that has a **HVR1** and/or **HVR2** as claimed. In other words, the specification does not disclose replacing the human *light chain* framework regions 1(FR1) subgroup III consensus sequence with the human *heavy chain* FR1 subgroup I and/or II consensus sequence at those position where the residues differ in any antibody.

Given the unlimited number of antibody and the amino acid substitutions in the heavy and light chains framework regions FR1, FR2, FR3, FR4 and mixture thereof, it is unpredictable

which amino acid substitution would improve the yield of the antibody for the claimed method. As evidence by the teachings of the specification, 25% of the antibodies in the claimed method fail to increase the yield of the antibody. Substituting the heavy chain FR1 subgroup III consensus sequence with subgroup I consensus sequence in the anti-IgE antibody resulted in a *decrease* rather than an increase in the yield of the antibody. The specification does not teach any in vitro assays to predict success in vivo folding and antibody assembly in all cells. The state of the art is such that even a single amino acid substitution in framework regions leads to unpredictable changes in the conformation and the binding specificity of the antibody. The framework residues are important in maintaining the structure of the CDRs and affecting the binding of the antibody. There is a structural effect, i.e. conformational changes of different amino acid (see Holmes et al, J Immunology 167: 296-301, 2001; PTO 892).

Foote et al (J Mol Biol 224: 487-499, 1992; PTO 892) teach replacing antibody framework residues affects the conformation of the hypervariable loops of the antibody (see page 497, col. 1, third paragraph, in particular). Accordingly, an undue experimentation would be required to determine how to practice the claimed invention.

(C) Enablement is not commensurate in scope with the claimed methods in how to produce any antibody or antigen binding fragment in high yield in cell culture by expressing any modified variable domain of the antibody or antigen binding fragment in a host cell wherein the modified variable domain has a substitution of at least one or more amino acid positions proximal to any cysteine residue that participates in an intrachain variable domain disulfide bond with a different amino acid as set forth in claims 50-74, and 100-103.

In order to produce any antibody in high yield in culture, the amino acid sequences with the appropriate sequence identifier (SEQ ID NO), the position of the amino acid proximal to the cysteine residue that participates in an intrachain variable domain disulfide bond and the type of amino acids to be substituted are required. Some of these amino acid positions proximal to disulfide bonded Cys residues have to be identified by inspection of crystal structure of the antibody follows by using graphics program. Crystallization of all antibodies has not been done.

The specification discloses only a method for producing anti-VEGF or antigen binding fragment thereof in high yield in cell culture comprising identifying at least one position selected form the group consisting of amino acid position 4 of the light chain, the amino acid position 71 of the light chain, the amino acid position 6 of the heavy chain, the amino acid position 34, and

amino acid position 78 of the heavy chain of anti-VEGF, substituting M at position 4 for L and F at position 71 for Y in the light chain with the appropriate sequence identifier and M at position 34 for I, E at position 6 for Q, M at position 34 for I, and A at position 78 for L in the heavy chain of anti-VEGF (with corresponding sequence identifier), expressing the construct pVG50 comprising the polynucleotide encoding the modified variable domain of the antibody having amino acid substitution M at position 4 for L and F at position 71 for Y in the light chain and M at position 34 for I, E at position 6 for Q, M at position 34 for I, and A at position 78 for L in the heavy chain and recovering the antibody or antigen binding fragment comprising the modified variable domain from the host cell (see specification page 90).

The specification does not teach modifying amino acid residues at position L33 and W35 in the light chain and L4, W36 and G104 in the heavy chain of any antibody as now claimed in claims 52-54. In fact, the specification at page 90 discloses these residues at position L33 and W35 in the light chain and L4, W36 and G104 in the heavy chain were NOT substituted because the amino acids in these position are highly conserved across all subgroup consensus sequences and have the same amino acid at that position. Further, the specification does not teach modifying amino acid residues at position 21, 22, 24, 25, 86, 87, 89 and 90 in the light chain variable domain of any antibody and/or any amino acid at position 20, 21, 23, 24, 90, 91, 93 and 94 in the heavy chain variable domain of any antibody (claims 56-57). There is insufficient guidance as to which amino acid to be substituted for each and every positions mentioned above. There is insufficient working example demonstrating modifying any amino acid at any one of the position 21, 22, 24, 25, 86, 87, 89 and 90 or combinations thereof in the light chain variable domain of any antibody and/or any amino acid at position 20, 21, 23, 24, 90, 91, 93 or combinations thereof within any one of CDRs of the heavy and light chain still maintains its structure and binds specifically to VEGF. The state of the art is such that even a single amino acid substitution within the CDR resulted in a lost of binding.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Given the unlimited combination and subcombination of amino acid substitutions within any one or more of the six CDRs from heavy and light chains including residues at position L33

and W35 in the light chain and L4, W36 and G104 in the heavy chain that are highly conserved across all subgroup consensus sequences as claimed, it is unpredictable which antibody produced by the claimed method still maintains its structure and binds specifically to VEGF. As such, an undue experimentation would be required to determine how to practice the claimed invention.

(D) Enablement is not commensurate in scope with claims as how to produce any antibody, any antibody such as humanized antibody or antigen binding fragment in high yield in cell culture by expressing any modified variable domain comprising at least one modified Framework regions (FR) such as FR1, FR2, FR3, "FR4" in heavy chain and/or FR1, FR2, FR3, "FR4" in light chain and "a mixture thereof" or all identified amino acid positions in all FR are each substituted (claims 1, 18, 19, 25, 29, 38, 49, 82, 92, 96, 104, 117, and 127).

In addition to the lack of guidance as to the structure of the amino acid sequences with the appropriate sequence identifier (SEQ ID NO), the location and the type of amino acids to be substituted within which framework region of immunoglobulin heavy and/or light chain mentioned above for the claimed method, there is insufficient guidance as to which one or more amino acids within the "mixture" of Framework regions such as FR4 and FR3, or FR4, FR3 and FR2 or FR4, FR3, FR2 and FR1 or FR2 and FR3, FR2 and FR4, or FR4 from heavy or light chain would resulted in increases the yield of antibody in the claimed method.

The specification at page 95-96 discloses that changing the heavy chain FR1 and FR2 of anti-VEGF antibody from human consensus subgroup III residues to the human consensus subgroup I residues increased antibody yield. The specification also discloses changing the heavy chain FR1, FR2 and FR3 of anti-VEGF to human consensus subgroup I increased antibody yield from *E coli* or CHO cells.

The specification does not teach modifying any one or more amino acids from any heavy chain FR1, FR2, FR3 and FR4 from any antibody or antigen binding fragment thereof, or any mixture thereof such as FR1 and FR4, FR2 and FR4, FR3 and FR4, or all four FR1, FR2, FR3 and FR4 increases antibody yield, much less modifying any one or more amino acids in the light chain FR1, FR2, FR3, FR4 or mixture thereof.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-74 and 82-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) the structure, i.e. amino acid sequence or the corresponding nucleotide encoding the heavy and light chain variable domain of any and all antibody, any antibody such as humanized antibody, chimeric antibody, monoclonal antibody, human antibody multispecific antibody diabodies an antibody generated by phage display or antigen binding fragment comprising at least any one modified FR for the claimed method as set forth in claims 1, 6, 7, 25-27, 32-34, 38-39, 44-45, 50-51, 60-61, 71-73, 82-86, 96-97, 100, 101, 104-110, 115, (2) which framework region (FR) from which heavy chain or light chain of which antibody to be modified as set forth in claims 1, 6, 12, 14, 16, 17, 18, 23, 29, 38-39, 92, and 117, (3) the type of amino acids to be substituted at position recited in claims 19, 20, 21, 22, 24, 42, 43, 48, 52-54, 56-57, 63-64, and 122-124 and (4) the position or location of the amino acids within the FR or mixture of FR to be substituted as set forth in claims 41, 49, 55, 100, 125, 126, and 127.

The specification discloses only two anti-VEGF antibodies designated VNERK, and Y0317. The specification discloses replacing the human *heavy chain* framework regions 1(FR1) subgroup III consensus sequence of SEQ ID NO: 3 in the specific VEGF antibody with the human *heavy chain* FR1 subgroup I consensus sequence of SEQ ID NO: 1 at those position where the residues differ resulted in increase in antibody yield. The specification also discloses a method for improving the yield of anti-VEGF antibody or humanized VEGF antibody or antigen binding fragment thereof in cell culture by substituting at least two amino acid residues in FR1 heavy chain of SEQ ID NO: 3 wherein the amino acid residue E at position 6 is substituted for Q and amino acid residue A at position 23 is substituted for K wherein the substitution increases the

yield of assembled anti-VEGF antibody about two fold or amino acid residue E at position 1 is substituted for Q, E at position 6 is substituted for Q, L at position 11 is substituted for V, Q at position 13 is substituted for K, L at position 18 is substituted for V, R at position 19 is substituted for K and A at position 23 for K (page 87). The heavy chain FR1 of the modified VEGF antibody is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO: 18; IgE).

With the exception of the specific amino acid substitutions in the specific anti-VEGF or antigen binding fragment thereof that increase antibody yield in cell culture for the claimed method, the other modification/substitution in any one or more heavy chain FR1, FR2, FR3 and FR4 or mixture thereof in the variable domains of other antibodies are not adequately described. In order to produce any antibody in high yield in culture, the amino acid sequences with the appropriate sequence identifier (SEQ ID NO) or the corresponding polynucleotides of immunoglobulin heavy and light chains variable domains (all six CDRs) including the framework regions are required. Further, the location and the type of amino acids to be substituted within the framework regions of immunoglobulin heavy and light chain of any and all antibody for the claimed method are not adequately described. This is particularly true for amino acid residues at position 21, 22, 24, 25, 86, 87, 89 and 90 in the light chain variable domain of any antibody and/or any amino acid at position 20, 21, 23, 24, 90, 91, 93 and 94 in the heavy chain variable domain of any antibody as set forth in claims 56-57.

With regard to "FR1, FR2, FR3, FR4 and mixture thereof", the specification at page 95-96 discloses that changing the heavy chain FR1 and FR2 of anti-VEGF antibody from human consensus subgroup III residues to the human consensus subgroup I residues increased antibody yield. The specification also discloses changing the heavy chain FR1, FR2 and FR3 of anti-VEGF to human consensus subgroup I increased antibody yield from *E coli* or CHO cells.

The specification does not adequately described the modification in any one or more amino acids within a heavy chain FR4 from any antibody or antigen binding fragment thereof. The specification does not adequately described the modification in any mixture such as heavy chain FR1 and FR4, FR2 and FR4, FR3 and FR4, or all four FR1, FR2, FR3 and FR4 of any antibody that would resulted in an increase in antibody yield, much less modifying any one or more amino acids in the light chain FR1, FR2, FR3, FR4 or mixture thereof of any antibody.

The specification discloses only a method of producing humanized anti-VEGF and a method of improve the yield of only anti-VEGF antibody or binding fragment thereof by

substituting the specific amino acids in the heavy chain FR1, FR2 and FR3 of the specific VEGF antibody, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of antibodies to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1, 8, 12, 28, 35, 39, 40, 61, 63, 64, 74, 88, 101, and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "HVR1", "HVR2" and "FR" in claim 1 indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. While abbreviation can be used in a claim, to avoid potential confusion, the first recitation of the abbreviation should be preceded by the full terminology, such as framework region (FR).

The method step in claims 8, 101, and 111 is indefinite because it is the expression vector comprising the polynucleotide encoding the variable domain of the antibody connected to the polynucleotide encoding the variable domain with modified FR, not the other way around as claimed.

The "HVR1 amino acid sequence" in claim 12 is ambiguous and indefinite because it is not clear whether the specific "HVR1 amino acid sequence" is referring to the human subgroup variable domain consensus sequence HVR1 or the corresponding HVR1 from the antibody or antigen binding fragment variable domain comprising the modified FR in base claim 1.

The "HVR1 amino acid sequence" in claim 28 is ambiguous and indefinite because it is not clear whether the specific "HVR1 amino acid sequence" is referring to the human subgroup variable domain consensus sequence HVR1 or the corresponding HVR1 from the antibody or antigen binding fragment variable domain comprising the modified FR in base claim 25.

The "both" in claim 35 has no antecedent basis in base claim 34. Base claim 34 recites the method further comprises a polynucleotide encoding a constant domain connected to the polynucleotide encoding the variable domain to form a polynucleotide encoding a full-length heavy *or* light chain.

The "said at least one FR" in claim 39, line 3 is ambiguous because this is the first time that said term is introduced in the claim. The term "said" should be deleted.

The "HVR1 amino acid sequence" in claim 40 is ambiguous and indefinite because it is not clear whether the specific "HVR1 amino acid sequence" is referring to the human subgroup variable domain consensus sequence HVR1 or the corresponding HVR1 from the antibody or antigen binding fragment variable domain comprising the modified FR in base claim 38.

The "first and second polynucleotide" in claim 61 has no antecedent basis in base claim 50 because the term "first and second polynucleotide" is not recited in base claim.

The "heavy chain variable domain" in claim 63 has no antecedent basis in base claim 60 or 51 because the term "heavy" is not recited in base claim.

The "light chain variable domain" in claim 64 has no antecedent basis in base claims 60 or 51 because the term "light" is not recited in base claim.

Claim 74 is incomplete for failing to achieve the goal set forth in the preamble.

The "HVR1 amino acid sequence" in claim 88 is ambiguous and indefinite because it is not clear whether the specific "HVR1 amino acid sequence" is referring to the human subgroup variable domain consensus sequence HVR1 or the corresponding HVR1 from the antibody or antigen binding fragment variable domain comprising the modified FR in base claim 82.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in—
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the

purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

13. Claims 1-18, 22-41, 44-49, 82-99, 104-121 and 125-127 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/45331 publication (filed Aug 6, 1997; PTO 1449).

The WO 98/45331 publication teaches a method of producing an antibody or antibody binding fragment that binds specifically to VEGF (see entire document, abstract, in particular). The reference method comprises expressing a variable domain of an antibody or antibody binding fragment in a prokaryotic host cell such as *E coli* or mammalian such as CHO cells wherein the reference heavy variable domain (HVR1) comprising at least one modified frame work region (FR) such as amino acid substitution for a different amino acids at variable heavy FR residues 37H, 49H, 67H, 69, 71, 73, 75, 76, 78, and/or 94 and recovering the antibody or antigen binding fragment (see entire document, see page 19, line 30-32, page 20, lines 11-21, page 26, in particular). The reference antibody is a humanized antibody (see page 19, line 20, page 25, in particular), a chimeric antibody, antibody generated by phage (see page 28, line 17, in particular), human antibody (see page 28, line 19, in particular), monoclonal (see page 23, line 21, in particular), a Fab, F(ab')2, scFv, or sc(FV)2, single arm antibody or single chain antibody (see 30, lines 3, page 11, in particular). The reference polynucleotide encodes the reference antibody in a vector and host cell (see claims 34-36, in particular). The reference CDRH1 amino acid sequence of GYX_1FTX_2YGMN wherein X1 is T or D, X2 is N or H is 100% identical to the claimed HVR1 amino acid sequence GYDFTHYGMN (SEQ ID NO: 18) (see claim 6 of WO publication, in particular). The reference framework region is FR1, FR2, FR3, FR4 and mixtures thereof (see page 20, lines 1-10, in particular). The reference further teaches modification in the variable light chain FR 1-4 comprising at least one modified framework region (FR) comprising amino acid substitution for a different amino acids derived from human consensus sequence of human kappa light chain subgroup I such as one or more of FR residues at position 4L, 46L, 71L (e.g., as in SEQ ID NO: 12) (see page 21, lines 15-32, in particular). Claims 15, 93, and 118 are included in this rejection because the reference teaches consensus heavy chain FR1 sequence compiled by Kabat and known in the art (see page 21, lines 20, in particular). Claims 16-17, 94-95, 119 and 120 are included in this rejection because given the reference method has the same modified FR amino acids using the same starting material, and the same method steps, reference method inherently increases the yield of the antibody or antibody fragment by at least 2 fold as compared to the unmodified antibody or antigen binding fragment. The reference anti-VEGF

antibody and binding fragment thereof is produced by a vector comprising the polynucleotide encoding a variable domain with a modified FR from either heavy chain, light chain or both and operably linked to a promoter, a heat stable sequence that can be direct secretion of the antibody to the periplasm and a terminator sequence (see page 38, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 1-18, 22-41, 44-49, 82-99, 104-121 and 125-127 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat NO. 6,884,879 B1 (filed Aug 6, 1997; PTO 892).

The '879 patent teaches a method of producing an antibody or antibody binding fragment that binds specifically to VEGF. The reference method comprises expressing a variable domain of an antibody or antibody binding fragment in a prokaryotic host cell such as *E coli* or mammalian such as CHO cells wherein the reference heavy variable domain (HVR1) comprising at least one modified frame work region (FR) such as amino acid substitution for a different amino acids at variable heavy FR residues 37H, 49H, 67H and recovering the antibody or antigen binding fragment (see entire document, col. 14, lines 34-67, bridging col. 15, lies 1-35, col. 17, lines 55-67, n particular). The reference antibody is a humanized antibody (see col. 9, line 19, in particular), a chimeric antibody, antibody generated by phage (see col. 19, lines 66-67, in particular), human antibody (see col. 20, line 51, in particular), monoclonal (see col. 9, lines 7, in particular), a Fab, F(ab')2, scFv, or sc(FV)2, single arm antibody or single chain antibody (see col. 7, lines 65-67, bridging col. 8, lines 1-64, in particular). The reference polynucleotide encodes the reference antibody (see reference SEQ ID NO: 110 and SEQ ID NO: 86, claims of 879 patent, in particular) and is expressed in a vector (see claim 2 of '879, in particular). The reference CDRH1 amino acid sequence of SEQ ID NO: 110 is 100% identical to the claimed HVR1 amino acid sequence GYTFTNYGIN (SEQ ID NO: 14) and the reference CDRH1 amino acid sequence of SEQ ID NO: 86 is 100% identical to the claimed GYDFTHYGMN (SEQ ID NO: 18) (see col. 15, lines 5-8, in particular). The reference framework region is FR1, FR2, FR3, FR4 and mixtures thereof (see col. 15, lines 28-40, col. 14, lines 40-46, in particular). The reference further teaches modification in the variable light chain FR 1-4 comprising at least one modified framework region (FR) comprising amino acid substitution for a different amino acids derived from human consensus sequence of human kappa light chain subgroup I such as one or more of FR residues at position 4L, 46L, 71L (e.g., as in SEQ ID NO: 12) (see col. 15, lines 28-55, see col. 16, lines 1-6, in particular). Claims 15, 93, and 118 are included in this rejection

because the reference teaches consensus heavy chain FR1 sequence compiled by Kabat and known in the art (see col. 14, lines 46-47, in particular). Claims 16-17, 94-95, 119 and 120 are included in this rejection because given the reference method has the same modified FR amino acids using the same starting material, and the same method steps, reference method inherently increases the yield of the antibody or antibody fragment by at least 2 fold compared to the unmodified antibody or antigen binding fragment. The reference anti-VEGF antibody and binding fragment thereof is produced by a vector comprising the polynucleotide encoding a variable domain with a modified FR from either heavy chain, light chain or both and operably linked to a promoter, a heat stable sequence that can be direct secretion of the antibody to the periplasm and a terminator sequence (see col. 25, lines 26-67, col. 26, lines 1-67, col. 27, lines 15-23, in particular). Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-3, 6, 10, 12, 14 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Forsberg et al (J Biol Chem 272(19): 12430-12436, May 1997; PTO 1449).

Forsberg et al teach a method of producing an antibody binding fragment such as Fab of a monoclonal antibody 5T4 that binds specifically to human tumor-associated antigen or a full length antibody such as the variable region of the reference Fab fused to sequences coding for the constant regions of murine IgG1/k antibody C242 (see page 12431, col. 1, first paragraph, in particular) in high yield in cell culture (see entire document, abstract, page 12430, col. 2, in particular). The reference method comprises expressing a variable domain of the antigen binding fragment (Fab) or the full-length antibody comprising amino acids substitutions such as Phe at position 10 changes to Ser (Phe-10-Ser), Ile-63-Ser, Tyr-67-Ser in framework region of the immunoglobulin light chain in a host cell such as *E coli*, recovering the antigen binding fragment of the antibody from the host cell such as *E coli* (see Expression of 5T4Fab-Sech in the Fermenter at page 12431, col. 1, Purification procedure, in particular). The reference selection of amino acid substitution is based on sequence alignment of the CDRs, comparing amino acid sequence of 5T4 to that of the known (consensus) antibody sequence such as C125 and selecting the amino acid residues identical with the corresponding sequence (see page 12433, Fig 1, in particular). The reference method resulted in a 15 fold increases in yield as compared to the unmodified antibody or antigen binding fragment (see page 12433, Figure 1, page 12434, col. 2, Discussion, Experimental Procedures, in particular). The reference amino acid substitution F to S at position 10 is found in the framework region 1 (FR1) (see Fig 1, comparison of the Light chain variable

domain, in particular). The reference amino acid substitutions from I to S at position 63 and from Y to S at position 67 are found in the framework region 3 (FR3), (see Fig 1, comparison of the Light chain variable domain, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-12, 14, 16-20, 22, 25-27, 29, 31-33, 36-38, 41-42, 44, 46-49, 71-73, 82-85, 87, 89-92, 94-99, 104-109, 111, 115, 117, 119-123, and 125-126 are rejected under 35 U.S.C. 102(b) as being anticipated by Presta et al (Cancer Res 57: 4593-4599, Oct 1997; PTO 1449).

Presta et al teach a method for producing an antibody binding fragment such as humanized Fabs by expressing a plasmid (vector) that contains DNA fragment encoding a variable domain such as all six CDRs from murine A.4.6.1 antibody (parent antibody) that binds specifically to VEGF and a modified framework regions wherein the modified framework region is from a consensus human k subgroup I light chain (see page 4593, col. 2, fourth full paragraph, page 4594, col. 1, Construction of humanized F(ab)s, in particular) in host cells such as prokaryotic *E coli* or mammalian CHO cells and recovering the antibody binding fragment comprising the modified framework from the host cell (see page 4594, col. 2, Construction, expression and Purification of Chimeric and Humanized IgG Variants, in particular). The reference method exhibits high yield antibody in one clone (see page 4594, col. 2, last paragraph, in particular). The reference method inherently contains all FR1, FR2, FR3 and FR4 since all six CDRs were used. Claim 18 is included in this rejection because the reference entire human framework region includes at least two amino acid positions in at least one of the FR have different amino acids from the murine framework regions. The reference method wherein at least two amino acid positions 6 and 23 of the heavy chain FR1 has been substituted from V to E at position 6 and C to A at position 23 (see page 4596, Col. Fig 1, "*" of variable heavy chain in F(ab)-12, in particular). Claims 71 and 72 are included in this rejection because at least one of the amino acid position proximal to a Cys residue were substituted in the reference methods where residue 71 from T to D in variable light chain F(ab)-12 and residue 34 from M to N in variable heavy chain (see page 4596, col. 1, Figure 1, in particular). Claims 16-17, 94-95, 119 and 120 are included in this rejection because given the reference method has the same modified FR amino acids using the same starting material, and the same method steps, reference method inherently increases the yield of the antibody or antibody fragment by at least 2 fold compared to

the unmodified antibody or antigen binding fragment. Thus, the reference teachings anticipate the claimed invention.

17. Claims 25-27, 28-29, 31, and 33-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Baca et al (J Biol Chem 272(16): 10678-10684, April 1997; PTO 892).

Baca et al teach a method for preparing a humanized antibody such as hu2.0 or hu2.10 or antigen binding fragment such as Fab fragment of A4.6.1 that binds to VEGF (see entire document, Experimental Procedures, in particular). The reference method comprises expressing VL and VH domains from mouse monoclonal antibody A4.6.1 and human constant domains where the framework residues (FRs) are derived from consensus sequence of the most abundant human subclasses, such as VLκ subgroup I and VH subgroup III (see page 10679, col. 1, in particular) in a host cell such as E coli strain 34B8 and recovering the antibody variable domain from the host cell (see page 10679, Expression and purification of humanized A4.6.1 Fab fragments, in particular). Baca et al teach the advantages of using the most common human VL and VH frameworks (the entire framework which contains all of the FR1, FR2, FR3 and FR4) are that it minimizes any potential immunogenicity of the humanized antibody, eliminates possible idiosyncracies associated with any one particular framework and has been demonstrated to give good yields of antibody when expressed recombinantly in either E coli or eukaryotic expression systems when go into large scale development for clinical application (see page 10679, col. 1, first full paragraph, in particular).

18. Claims 25-26, 28, and 33-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (J Mol Biol 293: 856-881, 1999; PTO 1449).

Chen et al teach a method for preparing a humanized antibody such as Fab-12 or Fab-IgG or antigen binding fragment such as Y0192 or Y0317 comprising expressing a variable domain comprising at least one FR sequence from a human consensus sequence and recovering the antibody variable domain Fab from host cell such as *E. coli,* which is a prokaryotic cell (see page 878, purification of Fab, in particular). The reference heavy chain region 1 (HVR1) of Y0317 antibody contains amino acid residues GYDFTHYGMN which is identical to the claimed SEQ ID NO: 18) (see Y0317, residues 26-36 in Figure 1, in particular) while the heavy chain region 1 (HVR1) of Y0197 antibody contains amino acid residues GYSITSGYSWN (SEQ ID NO: 14).

The reference full-length antibodies Y0317-IgG and Fab-12-IgG are expressed in CHO cell (mammalian cell) (see page 879, col. 1, reference therein, in particular).

19. Claims 21, 43, 50-70, 74, 100-103 and 124 are free of prior art.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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